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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,631	04/11/2005	Seiichi Araki	T0509.70011US00	5167

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WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
HUGHES, ALICIA R	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
08/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,631	ARAKI ET AL.	
	Examiner	Art Unit	
	Alicia R. Hughes	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims and Examination

Claims 15-19 are pending and the subject of this Office Action. Applicants cancelled claims 1-12 and 14 in the response filed on 10 April 2007.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 13 November 2006 has been entered.

Applicants' arguments filed on 10 April 2007 have been fully considered and are, in part, deemed to be persuasive regarding the previous rejection. Rejections not reiterated from this Office's previous action are hereby withdrawn. The rejections set forth herein constitute the complete set of rejections being applied to the instant application presently.

Response to Applicants' Arguments

Applicants argue that with regard to this Office's rejections made under 35 U.S.C. § 103(a): (1) the cited reference does not, in text or in diagram, teach or even suggest that riboflavin prevents increased cytokine production via the glutathione production pathway; and (2) the cited reference does not teach or suggest any relationship between riboflavin and cytokines. Examiner finds Applicants' responses wholly unpersuasive on both points based on the disclosures in Grimble, RF, "Effect of Antioxidative Vitamins on Immune Function with Clinical Applications. International J. Vitam. Nutr. Res., Vol. 67, No. 5, pages 312-320

(1997)[hereinafter referred to as "Grimble, et al"][1] coupled with the state of the art at the time that the invention was disclosed. *Please see generally*, Grimble, Robert, "Modification of Inflammatory Aspects of Immune Function by Nutrients," Nutrition Research, Vol. 18, No. 7, pages 1297-1317 (1998)[hereinafter referred to as "Gimble II"].

At the time the present invention was disclosed, it was well-known in the art that there is a direct correlation between the functionality of balanced cytokine production when reacting to an inflammatory response and the activity of the glutathione production pathway to limit the creation of excessive cytokines (See Grimble II, page 1308, latter portion of Conclusion paragraph 3).[2] It has been known for quite some time that "[c]ytokines play a crucial role as modulatory agents by which the activity of the system is changed and metabolic activity of the host directed towards provision of nutrients for the system from endogenous sources. Nutrient intake, prior to infection will influence the extent of endogenous nutrient provision." *Id.* Glutathione is defined as a "major endogenous antioxidant," and "[v]itamin B_6 and riboflavin participate in the maintenance of glutathione status" (See Abstract). Thus, endogenous nutrient provision, i.e. glutathione production, controls hyperactivity of cytokines, or hypercytokinemia, and "[v]itamin B6 and riboflavin participate in the maintenance of glutathione status" (See Abstract).

In short, "[d]eficiencies in vitamins E, B_6 and riboflavin reduce cell numbers in lymphoid tissues of experimental animals and produce functional abnormalities in the cell mediated immune response." *Id.* Thus, where there is a deficiency is riboflavin, endogenous nutrient

[1] Previously cited on PTO-892 of 24 March 2006.
[2] The high priority given to combating pathogens is necessary because of the speed with which pathogens multiply once established within the host. In general terms, bacterial cells multiply at least 50 times as rapidly as T cells

provision provided by glutathione will lack, thereby creating a heightened immne/inflammatory response that wields the over- or hyper-production of cytokines. Therefore, if a deficiency in riboflavin contributes to a heightened inflammatory response then it logically flows mechanistically that the presence of riboflavin has an inverse relationship with cytokine production as an immune response. It is the establishment of this relationship that makes the prior art rejection in Grimble, et al applicable to the instant invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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under favorable conditions. Thus, the provision of nutrients to allow the immune system to function correctly

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15-19 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-20 of copending Application No. 10/472,621. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully claimed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of treating hypercytokinemia comprising riboflavin wherein the '621 application claims a method for immunostimulation which when read in light of the diseases treated i.e. sepsis covers a method of administering riboflavin wherein hypercytokinemia will necessarily be treated as well in light of Grimble which teaches that antioxidative vitamins such as riboflavin prevent increased cytokine production via the glutathione production pathway. One of ordinary skill in the art would have found it obvious that a reduction in cytokine would be efficacious in the treatment of hypercytokinemia and

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cannot be left to chance.

consequently sepsis. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15 - 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble, et al as evidenced by Grimble II.

The teachings of Grimble II, *supra*, are incorporated herein by reference in total. This Office's previous teachings of Grimble, et al, in the Office Actions of 24 March 2006 and 06 October 2006 are also incorporated herein by reference, in total.

As noted previously, Grimble teaches that antioxidative vitamins such as riboflavin prevent increased cytokine production via the glutathione production pathway (see Abstract). One of ordinary skill in the art would have found it obvious that a reduction in cytokines would be efficacious in the treatment of hypercytokinemia. The use of a salt of riboflavin would have been obvious to one of ordinary skill in the art since salts dissociate and a salt of riboflavin would naturally dissociate into riboflavin and the salt. Moreover, to treat a patient, one would need to administer the riboflavin and such as claimed in claim 19 would have been obvious to

one of ordinary skill in the art. Thus, reference teaches and makes *prima facie* obvious how to use the claimed invention at the time that it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR of Public PAIR. Status information for unpublished applications is available through Public PAIR only. For information about the PAIR system, see http://pair-direct-uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

16 August 2007

Alicia Hughes

8/20/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER